REMARKS

The Office Action has rejected claims 38, 40-47, 54-56, 59, 60, 63-66 and 71-73 under 35 U.S.C. §103(a) as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 6,340,475 to Shell et al. ("Shell et al.") in view of the teachings of U.S. Patent No., 6, 387,403 to Seroff et al. ("Seroff et al."). In addition, claims 48 and 67-70 are rejected under 35 U.S.C. §103(a) as defining subject matter which is allegedly rendered obvious by the teachings in Shell et al. in view of Seroff et al. and further in view of the teachings of an article by Tobyn et al. in International Journal of Pharmaceuticals 1998, 169, 180-194 ("Tobyn et al.").

Applicant has amended the claims, which when considered with the comments herein, are deemed to place the present case in condition for allowance. Favorable action is respectfully solicited.

At the outset, before addressing the issues raised in the Office Action, it is noted that claim 1 was amended by reciting that the water insoluble or partially water insoluble cellulose in combination with maltodextrin further affects the release rate of the drug from the pharmaceutical composition. Support for the amendment is found in paragraph 48 of the instant application.

No new matter is added to the application.

Pursuant to the rejection of claims 38, 40-47, 54-56, 59, 60, 63-66 and 71-73 under 35 U.S.C. §103(a), the Office Action cites Shell et al. in combination with Seroff et al.

The present invention is directed to, inter alia, a sustained release pharmaceutical composition in solid oral dosage form having a core, said sustained release pharmaceutical composition comprising, in the core thereof, a homogeneous mixture comprising a

pharmaceutically effective amount of a drug, a sustained release carrier in an effective amount to retard the release of the drug from said composition when placed in an aqueous system, a water insoluble or partially water insoluble cellulose, maltodextrin and optionally a lubricating effective amount of a lubricant, wherein the weight ratio of the total amount of said water insoluble or partially water insoluble cellulose to maltodextrin ranges from about 50:1 to about 1:50 and wherein said water insoluble or partially water insoluble cellulose in combination with maltodextrin further affects the release rate of the drug from the pharmaceutical composition. As described in the specification, the sustained release carrier influences the release of the drug from the formulation. However, this release can be fine tuned by the additional combination of maltodextrin and the water insoluble or partially water insoluble cellulose, such as microcrystalline cellulose, silicified microcrystalline cellulose, and the like. As noted by Applicant in Paragraph 46 of the instant application, the presence of the excipient, the water insoluble or partially water insoluble cellulose had made it difficult to formulate controlled release tablets because they cause the disintegration of the tablet when in contact with an aqueous solution, causing the release of the medicament to be more rapid than desired. However, the inventor has found that this effect can be counteracted by the addition of maltodextrin. Thus, the present invention requires the interaction of maltodextrin with the water insoluble or partially water insoluble cellulose and the interaction of both with the drug. Further, the sustained release polymer generally controls the release of the drug from the pharmaceutical composition. Thus, all four of these components need to be in the core so that they can interact directly.

If the maltodextrin were not present in the core, it could not form a homogenous mixture, as defined herein, with the water insoluble cellulose or the partially water insoluble

cellulose, e.g., it could not interact with the water insoluble cellulose or partially water insoluble cellulose and counteract its effect in accelerating the release of the drug in the formulation. The cited prior art, alone or in combination, do not teach, disclose or suggest the presence of all four components in the core. None of the references contain all four of these components in a homogeneous mixture, as claimed. But, more importantly, the cited art do not teach, disclose or suggest that the maltodextrin and water insoluble or partially water insoluble cellulose in combination fine tune the release of the drug controlled by the sustained release polymer.

Shell et al. disclose oral dosage forms of drugs by incorporating them into polymeric matrixes comprised of hydrophilic polymers that swell upon imbibition of water to a size which is large enough to promote retention of the dosage form in the stomach during the feed mode. Examples of hydrophilic polymers include cellulose polymers and their derivatives, microcrystalline cellulose and xanthan gum. The Office Action refers to Example 4 of Shell et al. which discloses metformin controlled release dosage forms with various polymers such as xanthan gum, HPMC, hydroxyethyl cellulose and polyethylene oxide. Magnesium stearate may be included in the various formulations. The Office Action also refers to Example 10, which discloses a metformin dosage from comprising metformin, PEO, magnesium stearate and a coating comprised of HPMC.

However, Shell et al. do not disclose the inclusion of maltodextrin in the pharmaceutical composition, a position with which the Office Action concurs.

Seroff et al. disclose an osmotic dosage form adapted to release reboxetine at a uniform rate comprising

(a) a semipermeable membrane defining an internal compartment;

(b) an osmotic composition component comprising reboxetine and a carbohydrate within the internal compartment and

(c) a delivery orifice formed or formable in the semipermeable membrane through which the roboxetine is delivered.

The Office Action refers to Figure 2 and Example 4B. Figure 2 represent a bilayered core having two compartments. In Example 4B, the drug layer combines reboxetine, maltodextrin and stearic acid, and another layer, identified as the push layer, contains hydroxypropylmethylcellulose, which is hydrophilic and soluble in water and the barrier layer contains ethyl cellulose and stearic acid. Thus, Seroff et al. do not contain a water insoluble or partially water insoluble cellulose in the same layer as the maltodextrin. Moreover, the sustained release polymer, the drug, the water insoluble or partially water insoluble cellulose such as ethyl cellulose and the maltodextrin are in different layers. Since in Seroff et al., the maltodextrin and the water insoluble or partially water insoluble cellulose are in different layers, they cannot be part of a homogenous mixture and they cannot interact with each other so that together they cannot further control the release of the drug. Thus, Seroff et al. do not teach disclose or suggest the arrangement of elements, as claimed.

It is respectfully submitted that the Office Action has engaged in hindsight reconstruction of the art. Case law has held that it is impermissible within the framework of section '103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. Dennison Mfg. Co. v. Panduit Corp., 475 U.S. 809, 810 (1986); In re Wesslau, 353 F.2d 238, 251 (CCPA 1965). Here, the Office Action ignored the teachings of Seroff et al. As indicated hereinabove, Seroff et al. teach that

when maltodextrin is present in the drug layer, then the swellable polymers are in a different layer. But the USPTO ignored that teaching, and alleged that the combination suggests combining the maltodextrin in the drug layer with the other swellable hydrophilic polymers in the drug layer to support its obviousness rejection. Such a combination requires a substantial reconstruction and redesign of the elements in Seroff et al. as well as a change in the basic principles under which the reference's construction was designed to operate. See, In re Ratti, 270 F.2d 810, 813 (CCPA 1959). Seroff et al. do not teach or even suggest that the drug layer containing maltodextrin can also contain the hydrophilic polymers. Further, Seroff et al. also do not teach that the device therein contains water insoluble or partially water insoluble cellulose. More specifically, they teach that the osmopolymers are swellable hydrophilic polymers that imbibe an aqueous fluid. Water insoluble substances or partial water-insoluble polymers, such as the water-insoluble cellulose or partially water-insoluble cellulose, e.g., microcrystalline cellulose and starch, could not imbibe an aqueous fluid.

Moreover, the combination of Shell et al. and Seroff et al. do not teach disclose or suggest the present invention. As indicated hereinabove, Shell et al. do not teach, disclose or suggest the use of maltodextrin. On the other hand, Seroff et al. teach that when maltodextrin is present in the drug layer, then the swellable polymers are in a different layer. In other words, Seroff et al. teach that the hydrophilic polymers and the maltodextrin are in different layers. For example, Seroff et al in Example 4B refer to an internal compartment comprising a bilayered compressed core with a drug layer and a push layer, where the drug layer comprises, *inter alia*, roboxetine and maltodextrin and the push layer comprises polyethylene oxide, hydroxypropylmethylcellulose, which is water soluble and a barrier layer containing ethyl cellulose. Thus Seroff et al. do not disclose in Example 4B a water insoluble or partial water

insoluble cellulose together as a homogenous mixture with the drug, the maltodextrin and the sustained release hydrophilic carrier. Further, Seroff et al. do not have the drug, and the maltodextrin, the water insoluble or partial water insoluble cellulose and the sustained release carrier all mixed together as homogenous so that they interact with one another. As a result, the maltodextrin, for example, cannot interact with the water insoluble or partially water insoluble portion to act in combination to further control the release of the drug. When the maltodextrin is a different layer, there is no interaction between it and the drug, the insoluble or partially insoluble cellulose and the hydrophilic sustained release carrier.

Thus, the combination of Shell et al. and Seroff et al. do not teach, disclose or suggest the present invention.

Further, there is no teaching, or suggestion in either of the prior art references that the maltodextrin in combination with the water insoluble or water insoluble cellulose can affect the rate of release of the drug in the pharmaceutical composition. As indicated hereinabove, Shell et al. does not utilize maltodextrin in their formulation so that there is no recognition in Shell et al. of the effect of the interaction of these two components with the drug. Seroff et al. do not overcome this deficiency. More specifically, in Seroff et al, the maltodextrin is stated to be a chemical stabilizer for reboxetine. See, col. 13, line 57 of Seroff et al. Thus, the combination of Shell et al. and Seroff et al. do not teach, disclose or suggest the effect of the interaction of maltodextrin, the water insoluble or partial water insoluble cellulose and the drug, and the use thereof for fine tuning the release of a drug from a formulation, as the inventor has found.

Moreover, there is no motivation to combine the two prior art references in the first instance. Shell et al relate to drugs in general. On the other hand, Seroff et al. relate to a formulation containing reboxetine. As described hereinabove, it adds maltodextrin as a chemical

stabilizer for reboxetine. This appears to be an issue with reboxetine that is not contemplated with the drugs of Shell et al. Thus, there is no reason for one of ordinary skill in the art to combine the two art references in the manner suggested by the Office Action.

Therefore, for the reasons given hereinabove, this rejection is obviated; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claim 48 and 67-70, the Office Action cites Shell et al., Seroff et al. and Tobyn et al.

Applicant reiterates the comments hereinabove with respect to and Shell et al. and Seroff et al., the contents of which are incorporated by reference.

The Office Action is citing Tobyn et al. for the alleged substitution or equivalence of SMCC for microcrystalline cellulose.

Tobyn et al. do not address the inadequacies of Shell et al. and Seroff et al. It merely discloses that there is no discernable chemical or polymorphic difference between microcrystalline cellulose and silicified microcrystalline cellulose. Thus, Tobyn et al. do not address the deficiency of Shell et al. and Seroff et al. described hereinabove. The combination would at best suggest substituting silicified microcrystalline cellulose for microcrystalline cellulose. Accordingly, the combination would suggest a push layer containing soluble cellulose ether, the barrier layer containing ethyl cellulose, and the drug layer containing the drug and maltodextrin. The combination of Seroff et al. and Shell et al. and Tobyn et al. do not teach, disclose or suggest a sustained release formulation wherein the drug, the sustained release hydrophilic carrier, maltodextrin and the water insoluble or partially water soluble cellulose are all part of a homogenous mixture and are not in discrete layers. Further, if combined, the cited document would not suggest that the water insoluble or partially water insoluble cellulose

interact with one another to act in combination to further control the release of the drug, as claimed.

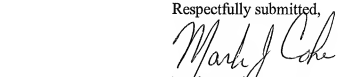
Moreover, there is no reason to combine the cited references in the manner suggested by the Office Action in the first instance for the reasons given hereinabove. More specifically, none of the cited art recognize that maltodextrin or silicified maltodextrin prolongs the release of the drug from the formulation or that its interaction with a water insoluble or partial water insoluble cellulose ether can be used to fine tune the release of the drug. Neither Shell et al. nor Seroff et al. recognize this effect. Shell et al. recognize that microcrystalline cellulose is an excipient. There is no recognition therein that it can increase the rate of release of the drug from the formulation. Seroff et al. teach that maltodextrin stabilizes reboxetine. There is no recognition that it retards the release of the drug. Tobyn discloses that silicified microcrystalline cellulose has a number of pharmaceutical advantages, but none are linked to the advantages described in the instant specification of retarding the rate of release of the drug or when interacting with maltodextrin, fine tuning the rate of release of the drug. Further, silicified microcrystalline cellulose is a known pharmaceutical excipient, and it is impermissible hindsight for the Office Action to assert that it would be obvious to use it in these formulations for the purpose of the present invention. In fact, the specification asserts that silicified microcrystalline cellulose without maltodextrin has a more rapid release of drug product, a property which was not described in either of the cited art.

Thus, the improvement in the pharmaceutical composition is more than predictable use of the elements according to their established functions. As a result, the present invention is patentable.

Therefore, for the reasons given herein, the present rejection is obviated; withdrawal thereof is respectfully requested.

Thus, in view of the amendments to the claims and the Remarks herein, it is respectfully submitted that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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